



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<b>(21) International Application Number:</b> PCT/GB92/01299 <b>(22) International Filing Date:</b> 16 July 1992 (16.07.92)  <b>(30) Priority data:</b> 9115740.4                      20 July 1991 (20.07.91)                      GB  <b>(71) Applicant (for all designated States except US):</b> SMITH-KLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).  <b>(72) Inventor; and</b> <b>(75) Inventor/Applicant (for US only) :</b> HOWSON, William [GB/GB]; Parke-Davis Research Unit, Addenbrookes Hospital, Cambridge CB2 2QB (GB).  <b>(74) Agent:</b> SMITHKLINE BEECHAM; Corporate Patents, Mundells, Welwyn Garden City, Hertfordshire AL7 1EY (GB).		<b>(81) Designated States:</b> AU, CA, JP, KR, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LU, MC, NL, SE).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> S-(3-(4(5)-IMIDAZOLYL)PROPYL)ISOTHIOUREA AS SELECTIVE TRHISTOMINE H3 RECEPTOR ANTAGONIST  <b>(57) Abstract</b>  Use of an isothiourea derivative as a histamine H <sub>3</sub> -antagonist.		

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S-(3-(4(5)-IMIDAZOLYL)PROPYL)ISOTHIIOUREA AS SELECTIVE TRHISTOMINE H<sub>3</sub>  
RECEPTOR ANTAGONIST

The present invention relates to pharmaceutical  
5 compositions comprising an imidazole derivative, their use in  
the manufacture of medicaments having histamine H<sub>3</sub>-antagonist  
activity and a method of blocking histamine H<sub>3</sub>-receptors by  
administering them.

10 Histamine, a physiologically active compound  
endogenous in mammals, exerts its action by interacting with  
certain sites called receptors. One type of receptor is  
known as a histamine H<sub>1</sub>-receptor (Ash and Schild, Brit. J.  
Pharmac. Chemother. 27 427 (1966)) and the actions of  
15 histamine mediated through these receptors are blocked by H<sub>1</sub>-  
antagonists such as mepyramine. A second type of receptor is  
known as the histamine H<sub>2</sub>-receptor (Black et al., Nature  
1972, 236, 385) which is not blocked by mepyramine but by H<sub>2</sub>-  
antagonists such as burimamide or cimetidine. A third type  
20 of receptor known as the histamine H<sub>3</sub>-receptor has more  
recently been identified (e.g. Arrang et al., Nature 1987,  
327 , 117 and Van der Werf et al., (1989) Trends Pharmacol.  
Sci. 10, 159) which is stimulated by H<sub>3</sub>-agonists such as (R)-  
 $\alpha$ -methylhistamine and blocked by H<sub>3</sub>-antagonists such as  
25 thioperamide.

US-A-3759944 discloses isothioureia derivatives which  
are described as acting at histamine receptors other than the  
H<sub>1</sub>-receptor and are of utility in inhibiting certain actions  
30 of histamine which are not inhibited by H<sub>1</sub>-antagonists such  
as the inhibition of histamine-stimulated secretion of  
gastric acid. A particular isothioureia described is S-[3-  
(4(5)-imidazolyl)propyl]isothioureia dihydrobromide. This  
compound is also disclosed in Eur. J. Med. Chem.-Chim. Ther.,  
35 21(4), 305-9 (1986) wherein it is described as being a weak  
partial H<sub>1</sub>-agonist and a weak H<sub>2</sub>-agonist.

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It has now been discovered that the above named imidazole compound is a highly potent selective histamine H<sub>3</sub>-antagonist.

5           Accordingly the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and S-[3-(4(5)-imidazolyl)propyl]-isothiourea or a pharmaceutically acceptable salt thereof in an amount sufficient to block selectively histamine H<sub>3</sub>-  
10 receptors.

          In another aspect the present invention provides the use of S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof in the manufacture  
15 of a medicament having histamine H<sub>3</sub>-antagonist activity.

          In a further aspect this invention provides a method of blocking histamine H<sub>3</sub>-receptors in a host in need thereof which comprises administering an effective amount to block  
20 said receptors of S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof.

          Pharmaceutically acceptable salts include those formed with hydrochloric, hydrobromic, sulphuric, phosphoric,  
25 acetic, citric, maleic, lactic, ascorbic, fumaric, oxalic, methanesulphonic and ethanesulphonic acids.

          In order to use S-[3-(4(5)-imidazolyl)propyl]-isothiourea or a pharmaceutically acceptable salt thereof for  
30 the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

          S-[3-(4(5)-imidazolyl)propyl]isothiourea and its  
35 pharmaceutically acceptable salts can be administered in standard manner for example orally, sublingually, parenterally, transdermally, rectally, via inhalation or via buccal administration.

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S-[3-(4(5)-imidazolyl)propyl]isothiourea and its pharmaceutically acceptable salts which are active when given orally or via buccal administration can be formulated appropriately in dosage forms such as liquids, syrups, tablets, capsules and lozenges. An oral liquid formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations can be used. Examples of such carriers include magnesium stearate, starch, celluloses, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions can be considered, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound or salt in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil or solubilising agent, for example polyethylene glycol, polyvinyl-pyrrolidone, 2-pyrrolidone, cyclodextrin, lecithin, arachis oil, or sesame oil.

A typical suppository formulation comprises S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats or their synthetic analogues.

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example

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a cream, ointment, lotion or paste or are in the form of a medicated plaster, patch or membrane.

Typical compositions for inhalation are in the form of  
5 a solution, suspension or emulsion that may be administered in the form of an aerosol using a conventional propellant such as dichlorodifluoromethane or trichlorofluoromethane, or are in the form of a powder for insufflation.

10 Preferably the composition is in unit dosage form, for example a tablet, capsule or metered aerosol dose, so that the patient may administer to himself a single dose.

Each dosage unit for oral administration contains  
15 suitably from 0.1 mg to 50 mg, and preferably from 1 mg to 25 mg, and each dosage unit for parenteral administration contains suitably from 0.1 mg to 25 mg, of S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof calculated as the free base.

20 The daily dosage regimen for oral administration is suitably about 0.1 mg to 200 mg, preferably 1 mg to 100 mg, of S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof calculated as the  
25 free base. The daily dosage regimen for parenteral administration is suitably about 0.1 mg to 100 mg, for example about 1 mg to 40 mg, of S-[3-(4(5)-imidazolyl)-propyl]isothiourea or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient  
30 may be administered as required for example from 1 to 4 times a day or by infusion. For administration by inhalation dosages are controlled by a valve, are administered as required and for an adult are conveniently in the range 0.1-5.0 mg of S-[3-(4(5)-imidazolyl)propyl]isothiourea or a  
35 pharmaceutically acceptable salt thereof.

The compounds of this invention may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially. Conveniently the

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compounds of this invention and the other active compound or compounds are formulated in a pharmaceutical composition. For example diazepam may be included in pharmaceutical compositions comprising S-[3-(4(5)-imidazolyl)propyl]-  
5 isothiurea.

The histamine H<sub>3</sub>-antagonist activity of S-[3-(4(5)-imidazolyl)propyl]isothiurea was assessed by a method similar to that described by Trzeciakowski (1987), J.  
10 Pharmacol. Exp. Ther., 243, 874-880. Inhibition of the electrically evoked twitch responses of the guinea-pig ileum by histamine H<sub>3</sub>-receptor agonists was studied by addition of graded concentrations of (R)- $\alpha$ -methyl-histamine (in volumes of 25  $\mu$ l or 79  $\mu$ l) to the organ bath in a sequential manner.  
15 Each concentration of agonist was washed out of the bath when the response had reached equilibrium. A four minute period was allowed between each addition of the compound. In the antagonist studies a ten minute period was used for the antagonist equilibration time. Antagonist activity was  
20 quantified by the ability of the compound to block the inhibitory effect of (R)- $\alpha$ -methylhistamine on the twitch response.

The concentration of compound which caused 50% antagonism of  
25 the inhibitory effect of (R)- $\alpha$ -methylhistamine on the twitch response is given as the IC<sub>50</sub> (nM). The following results were obtained:

Compound of formula (1)	IC <sub>50</sub> (nM)
S-[3-(4(5)-imidazolyl)-propyl]isothiurea	7
Thioperamide	6.4

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The activity of S-[3-(4(5)-imidazolyl)propyl]-isothiourea at the histamine H<sub>1</sub>- or H<sub>2</sub>-receptor was assessed substantially as described by Parsons et al., Agents and  
5 Actions, 1976, 7(1), 31. Concentrations up to 10<sup>-5</sup> M had no agonist or antagonist activity at histamine H<sub>1</sub>- and H<sub>2</sub>-receptors.

The above results indicate that S-[3-(4(5)-imidazolyl)-  
10 propyl]isothiourea is a highly potent selective histamine H<sub>3</sub>-antagonist, being about 1000 times more potent at the histamine H<sub>3</sub>-receptor than at either the histamine H<sub>1</sub>- or H<sub>2</sub>-receptor.

15 Antagonists of the histamine H<sub>3</sub>-receptor are believed to stimulate the synthesis and release of neurotransmitters such as histamine and are therefore likely to increase neurotransmitter release in the digestive tract and in the nervous, cardiovascular and immune systems. They are likely  
20 to have a psychotropic action and have utility in cognitive disorders including the treatment of Alzheimer's disease and age-associated memory impairment.

The following example serves to illustrate a  
25 pharmaceutical composition of this invention.



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**Example 1**

A pharmaceutical composition for oral administration is prepared containing:

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		% by weight
A	S-[3-(4(5)-imidazolyl)propyl]isothiourea	55
	Dibasic calcium phosphate dihydrate	20
	Approved colouring agent	0.5
	Polyvinylpyrrolidone	4.0
B		% by weight
	Microcrystalline Cellulose	
	Maize Starch	8.0
	Sodium glycollate	4.0
	Magnesium Stearate	0.5

by mixing together the ingredients A (substituting lactose or microcrystalline cellose for dibasic calcium phosphate dihydrate if desired), adding a concentrated solution of polyvinylpyrrolidone and granulating, drying and screening the dried granules; adding the ingredients B to the dried granules and compressing the mixture into tablets containing 10 mg, 25 mg or 50 mg of the free base.

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## Claims

1. A pharmaceutical composition which comprises a pharmaceutically acceptable carrier and S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof in an amount sufficient to block selectively histamine H<sub>3</sub>-receptors.  
5
2. A pharmaceutical composition according to claim 1 adapted for oral administration wherein each dosage unit comprises from 0.1 mg to 50 mg of S-[3-(4(5)-imidazolyl)-propyl]isothiourea.  
10
3. A pharmaceutical composition according to claim 1 adapted for parenteral administration wherein each dosage unit comprises from 0.1 mg to 25 mg of S-[3-(4(5)-imidazolyl)propyl]isothiourea.  
15
4. The use of S-[3-(4(5)-imidazolyl)propyl]-isothiourea or a pharmaceutically acceptable salt thereof in the manufacture of a medicament having histamine H<sub>3</sub>-antagonist activity.  
20
5. A method of blocking histamine H<sub>3</sub>-receptors in a host in need thereof which comprises administering an effective amount to block said receptors of S-[3-(4(5)-imidazolyl)propyl]isothiourea or a pharmaceutically acceptable salt thereof.  
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# INTERNATIONAL SEARCH REPORT

International Application No. 40

PCT/GB 92/01299

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.C1.5                      A 61 K 31/415		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.C1.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	US,A,3759944 (J.W. BLACK et al.) 18 September 1973, see whole document (cited in the application)	1-3
A	---	4,5
A	Agents and Actions, vol. 18, nos. 1/2, 1986, Birkhäuser Verlag, (Basel, DE), G.J. STERK et al.: "The influence of guanidino and isothioureia groups in histaminergic compounds on H2-activity", pages 137-140, see whole document, especially page 138, last paragraph	1-5
A	EP,A,0197840 (INSERM) 15 Oktober 1986, see whole document <div style="text-align: right;">-/-</div>	1-5
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
24-09-1992	20.10.92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE		

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0420396 (SMITH KLINE & FRENCH LAB. LTD) 3 April 1991, see whole document -----	1-5

# ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. ...

GB 9201299

SA 62460

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 14/10/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A- 3759944	18-09-73	US-A- 3818097	18-06-74
EP-A- 0197840	15-10-86	FR-A- 2579596	03-10-86
		JP-A- 61267574	27-11-86
		US-A- 4707487	17-11-87
EP-A- 0420396	03-04-91	JP-A- 3058924	14-03-91
		US-A- 5047418	10-09-91